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## Accepted Manuscript

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# **Clinical effectiveness of bisphosphonates for the prevention of fragility fractures: a systematic review and network meta-analysis**

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## Abstract

### Objectives:

To assess the relative efficacy of bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid) for the treatment of osteoporosis using network meta-analysis (NMA).

### Methods:

A systematic review of the literature was conducted using PRISMA guidelines. A network meta-analysis was used to determine the relative efficacy of treatments on four fracture outcomes (vertebral, non-vertebral, hip and wrist) and percentage change in femoral neck bone mineral density (BMD). Treatment effects were modelled using an exchangeable treatment effects model. Heterogeneity in treatment effects was explored by considering potential treatment effect modifiers using meta-regression. Where appropriate, inconsistency between direct and indirect evidence was assessed using node-splitting.

### Results:

46 randomised controlled trials (RCTs) were identified. Twenty seven RCTs provided fracture data and 35 RCTs provided BMD data for analysis. Zoledronic acid was associated with the greatest treatment effect on vertebral fractures (HR 0.41, 95% CrI: 0.28,0.56) and percentage change in BMD (3.21, 95%: CrI 2.52,3.86) compared to placebo. The greatest treatment effect on non-vertebral and wrist fractures was given by risedronate (HR 0.72, 95%: CrI 0.53,0.89 and HR 0.77, 95%: CrI 0.44,1.24, respectively). For hip fractures the greatest treatment effect was given by alendronate (HR 0.78, 95% CrI: 0.44,1.30).

### Conclusions:

All treatments examined were associated with beneficial effects on fractures and femoral neck BMD relative to placebo. For vertebral fractures and percentage change in femoral neck BMD the treatment effects were statistically significant for all treatments. Pairwise comparisons between treatments indicated that no active treatment was statistically significantly more effective than any other active treatment for fracture outcomes. There was some heterogeneity in treatment effects between studies suggesting differential treatment effects according to study characteristics; however, there was no evidence of differential treatment effects with respect to gender and age.

## 1. Introduction

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in susceptibility to fragility fracture (a broken bone resulting from a fall at standing height or less). Fractures cause significant pain, disability and loss of independence and can be fatal [1]. Osteoporosis affects over three million people in the UK [2]. Worldwide, osteoporosis causes more than 8.9 million fractures annually [3].

Bisphosphonates are a class of drug prescribed for the prevention of fragility fractures. In the UK, the National Institute for Health and Care Excellence (NICE) recommends alendronate for postmenopausal women at risk of fragility fracture for both primary prevention [4] and secondary prevention [5]. Risedronate is recommended for women who cannot take alendronate [4-6]. These recommendations currently do not include men and do not evaluate ibandronate or zoledronic acid. Clinical effectiveness is considered by assessing fracture incidence as the primary efficacy outcome (vertebral, non-vertebral, hip and wrist) in randomised controlled trials (RCTs).

Comparative effectiveness was evaluated using a network meta-analysis (NMA) to allow a comprehensive analysis of all evidence on all relevant treatments. NMAs can be used to combine direct and indirect evidence about treatment effects across RCTs that share at least one treatment in common with at least one other study [7]. Evidence reviews exist that evaluate alendronate, ibandronate, risedronate and zoledronic acid along with other treatments for osteoporosis and that have pooled fracture data across studies in a NMA [8-11]. However, analyses are often limited by sparse data for specific skeletal sites and treatments. For example Ellis et. al [8] Jansen et.al [10] and Murad et. al. [11] do not include wrist fractures, and in [9] comparisons for this site are not available for ibandronate or zoledronic acid. Although the reporting of specific skeletal sites is disparate across the RCT evidence base, the majority also report change in femoral neck bone mineral density (BMD). Femoral neck BMD may be considered as a surrogate for fracture outcomes but, despite this, we are not aware of a published NMA for the effect of bisphosphonates on change in BMD.

The purpose of the present study was to undertake a systematic review of the evidence base for alendronate, ibandronate, risedronate and zoledronic acid in the treatment of osteoporosis

and to present a NMA of both fracture outcomes and change in femoral neck BMD, from RCTs in men and women.

## **Materials and Methods**

### **2.1. Review methods**

The review was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (<http://www.prisma-statement.org/>). Searches were undertaken in MEDLINE and other databases to end of September 2014. Contact with experts and reference checking was also undertaken to identify studies. The results of the searches were sifted to identify potentially relevant studies that satisfy the inclusion/exclusion criteria by two independent reviewers (MMSJ and EG). RCTs in men and women that evaluated alendronate, ibandronate, risedronate or zoledronic acid compared with each other or compared with placebo or other non-active treatments, and that reported fracture outcomes and/or BMD were eligible for inclusion. The primary outcomes for the NMA were, hip vertebral, non-vertebral, wrist, proximal humerus fractures and fragility fracture at other sites, and bone mineral density at the femoral neck assessed by dual energy X-ray absorptiometry (DXA). Details of outcome definition for each study are provided in Supplementary Table 2. Data were extracted from included studies by two independent reviewers (MMSJ and EG). Data were extracted using a piloted data extraction form. Methodological quality of RCTs identified for inclusion was assessed using the Cochrane Collaboration risk of bias assessment criteria [12].

#### **1.1. Methods for the network meta-analysis**

A NMA was conducted for each of the four main fracture types, and for femoral neck BMD. An exchangeable treatment effects model was used (i.e. class effects model) where the treatment effects are assumed to arise from a common distribution according to the class of drug. For fracture outcomes, treatment effects are presented as hazard ratios (HR) relative to placebo, with a HR less than one reflecting a reduced risk of fracture relative to the comparator treatment. For femoral neck BMD, treatment effects are presented as the difference in mean percentage change from baseline in BMD relative to placebo after 1.8

years follow-up (the average duration of follow-up in these studies). Full details of the statistical model are given in the supplementary information.

Where appropriate, heterogeneity in treatment effects was explored by considering potential treatment effect modifiers using meta-regression [13]. Baseline risk/response can be used as a proxy for differences in patient characteristics across trials that may be modifiers of treatment effect. Adjustment for baseline risk/response was assessed using the method of Achana *et al.* [14].

Potential inconsistency between direct and indirect evidence was assessed using the node-splitting method of Dias *et al.* [15]. In the case of fracture data, inconsistency was assessed for vertebral fractures only. For non-vertebral fractures, no indirect evidence was available. For hip and wrist fractures, an assessment of inconsistency was not performed because the direct evidence about treatment effect in the active comparator study is provided by one small study [16] with no events in each baseline arm, thereby providing imprecise evidence of treatment effect.

All analyses were conducted in the freely available software package WinBUGS [17] and R [18], using the R2Winbugs [19] interface package. Convergence to the target posterior distributions was assessed using the Gelman-Rubin statistic, as modified by Brooks and Gelman [20], for two chains with different initial values. For all outcomes, a burn-in of 50,000 iterations of the Markov chain was used with a further 20,000 iterations retained to estimate parameters. Samples from the posterior distributions exhibited moderate correlation between successive iterations of the Markov chain so were thinned by retaining every 10<sup>th</sup> sample.

The absolute goodness of fit was checked by comparing the total residual deviance to the total number of data points included in an analysis. The deviance information criterion (DIC) provides a relative measure of goodness-of-fit that penalises complexity and was used to compare different models for the same likelihood and data [21]. Lower values of DIC are favourable, suggesting a more parsimonious model.

Results are presented using the posterior median treatment effects, 95% credible intervals (CrI) and 95% prediction intervals (PrI). The probability of each intervention ranking was

computed by counting the proportion of iterations of the Markov chain in which each intervention had each rank [22]. The treatment effects of each intervention compared to placebo together with the median rank and 95% CrI are displayed in forest plots for each outcome.

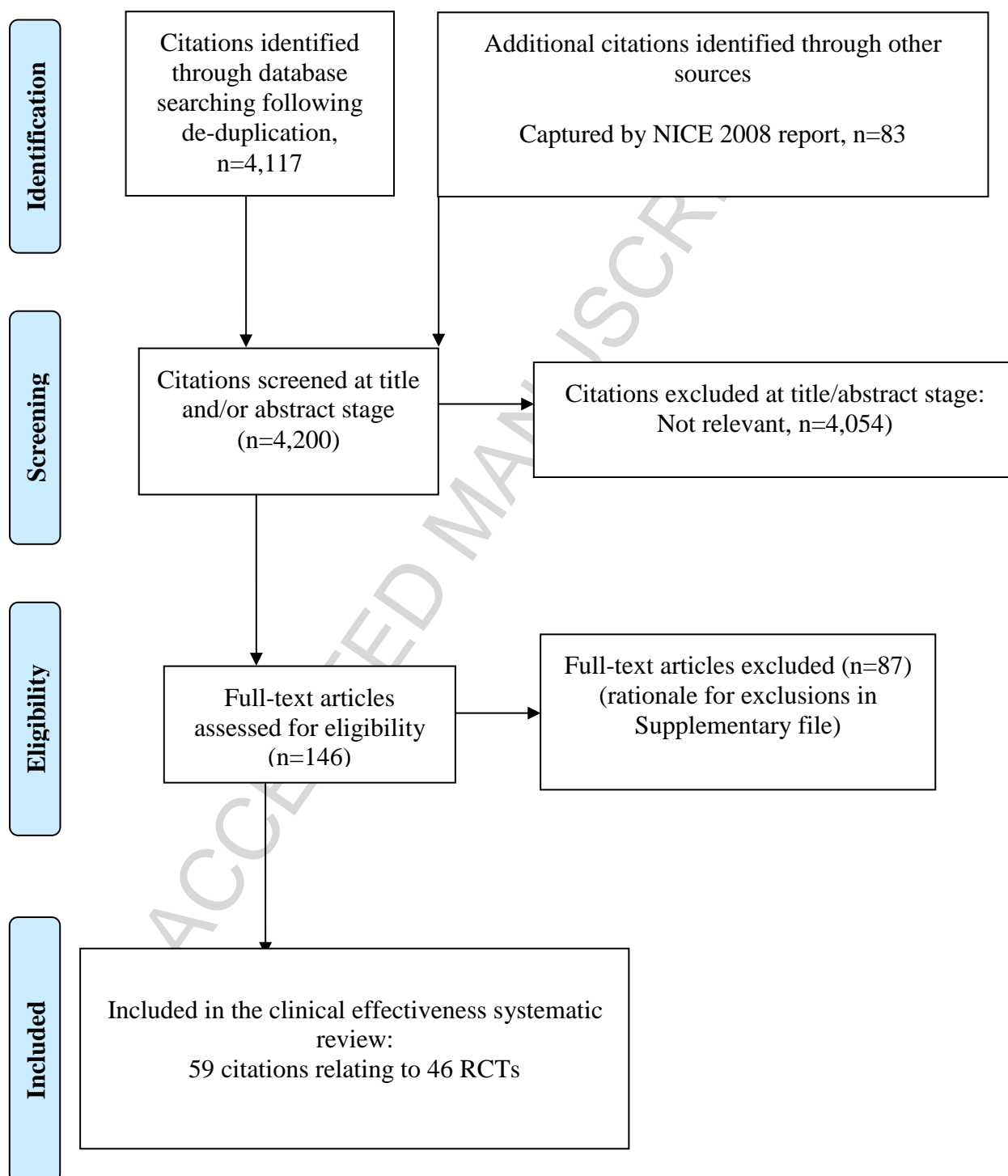
## **2. Results**

### **2.1. Search results**

The searches identified 4,117 potentially relevant citations from searches of electronic databases after removal of duplicates. A further 83 citations were identified from an existing evidence review commissioned by NICE [23]. Of these records, 4,054 were excluded at the title or abstract stage. Full texts of 146 citations were obtained for scrutiny. Of these, 87 citations were excluded (the Table of excluded studies with reason for exclusion is presented as Supplementary Table 1). A total of 46 RCTs [16, 24-68] reported across 59 citations were included in the review. The study selection process is fully detailed in the PRISMA flow diagram in Figure 1.



Figure 1: Flow diagram of study selection process (adapted from PRISMA)



Details of the included RCTs are provided in Supplementary Table 2. Alendronate was evaluated against placebo in seventeen RCTs. Daily oral ibandronate was evaluated against placebo in three RCTs and against i.v. administration in one RCT. Daily administration of oral ibandronate was evaluated against monthly administration in one RCT. Risedronate was evaluated against placebo in twelve RCTs, and zoledronic acid was evaluated against placebo in four RCTs. One RCT evaluated alendronate compared with ibandronate, five RCTs evaluated alendronate compared with risedronate, one RCT evaluated zoledronic acid compared with alendronate, and one RCT evaluated zoledronic acid compared with risedronate. The maximum trial duration was 48 months. Details of inclusion and exclusion criteria for participants, number of patients randomised, outcomes reported and fracture and BMD assessments across the included studies are presented in Supplementary Table 2.

From the Cochrane risk of bias assessment, attrition  $\geq 10\%$  across treatment groups was evident for 29 (63%) of the included RCTs. Five trials were reported as either open label or single blind and were considered at high risk of performance bias. Blinded outcome assessment was only reported by 13 (29%) trials. A summary of all risk of bias assessed by RCT is reported in Supplementary Figure 1. A summary of each risk of bias item is presented in Supplementary Figure 2.

## **2.2. Results of the network meta-analysis**

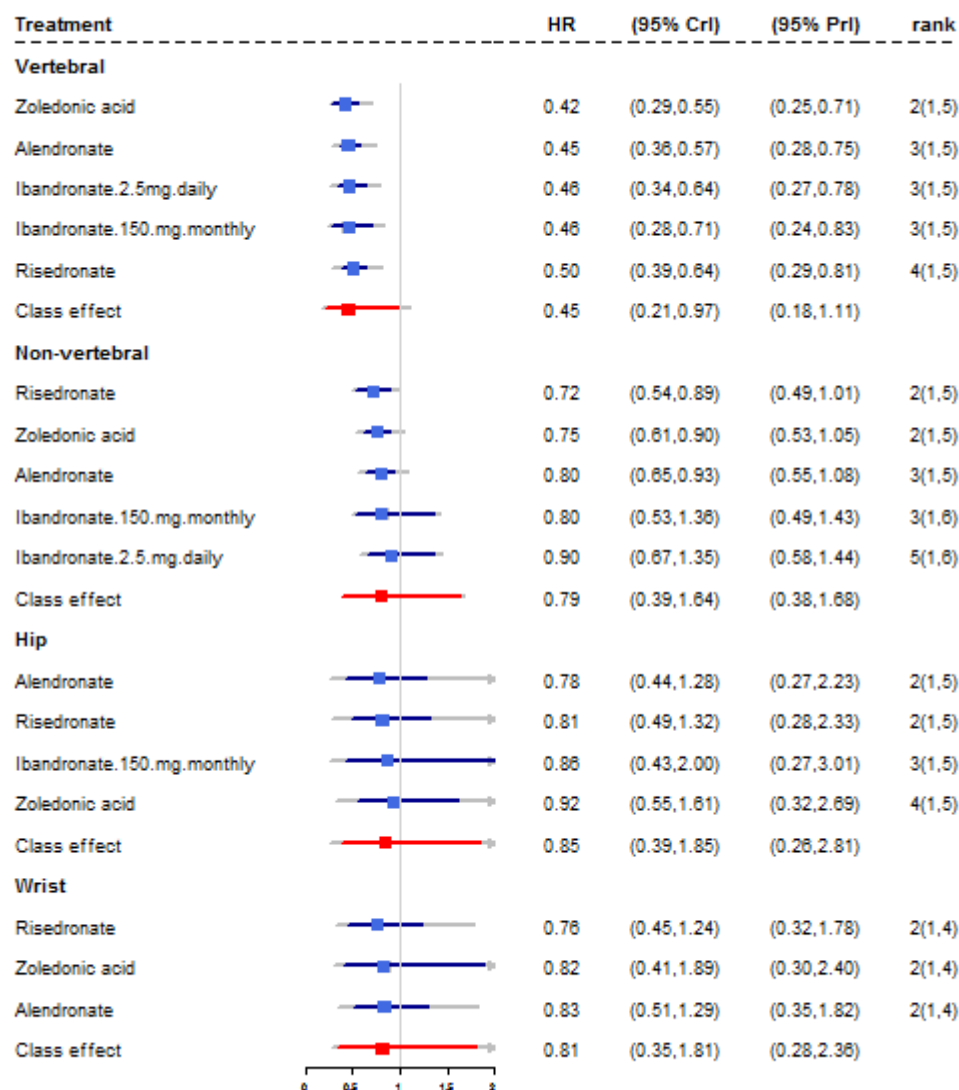
A total of 27 RCTs provided suitable fracture data for inclusion in the NMA and 35 RCTs provided suitable data for inclusion in the femoral neck BMD NMA. Network diagrams for each of the outcomes are presented in the supplementary material, along with an assessment of model fit.

### **3.2.1. Vertebral fractures**

Vertebral fracture data were available from 21 RCTs, each comparing two treatments. The effects of each treatment relative to placebo are presented in Figure 2 and pairwise comparisons between treatments are provided in Supplementary Table 3. All treatments were associated with beneficial treatment effects relative to placebo. Zoledronic acid was associated with the greatest effect, HR 0.41 (95% CrI: 0.28, 0.56). Zoledronic acid was likely to be the most effective treatment (probability 0.44 of being the most effective; median rank 2

(95% CrI: 1, 5)), although there was insufficient evidence to differentiate between the interventions. The hazard ratio for a randomly chosen study for a new bisphosphonate is 0.45 (95% PrI: 0.18, 1.11), with the reported prediction interval allowing for both between-study and between-treatment heterogeneity.

**Figure 2: Hazard ratios and 95% credible intervals (CrI) for the effect of treatment relative to placebo by fracture outcomes.**



Blue - pooled effects; Red - class effects; Grey: 95% prediction intervals (PrI). Median ranks and 95% CrI are displayed in the right hand column.

Within the network there were three treatment pairs for which both direct and indirect comparison were available (since the risedronate versus alendronate comparison is contributed by one small study with a zero count in the control arm, loops including this comparison were not included in the assessment of inconsistency). None of the comparisons showed significant evidence of inconsistency (Supplementary Table 11).

### 3.2.2. Non-vertebral fractures

Non-vertebral fracture data were available from 14 RCTs. All treatments were associated with beneficial treatment effects relative to placebo. Risedronate was associated with the greatest effect, HR 0.72 (95% CrI: 0.54, 0.89). Risedronate was likely to be the most effective treatment (probability 0.47 of being the most effective; median rank 2 (95% CrI: 1, 5)), although there was insufficient evidence to differentiate between the interventions. The hazard ratio for a randomly chosen study for a new bisphosphonate is 0.79 (95% PrI: 0.39, 1.64), allowing for both between-study and between-treatment heterogeneity.

### 3.2.3. Hip fractures

Hip fracture data were available from 10 RCTs. All treatments were associated with beneficial treatment effects relative to placebo, although the true treatment effects were inconclusive relative to placebo. Alendronate was associated with the greatest effect, HR 0.78 (95% CrI: 0.45, 1.28). Alendronate was likely to be the most effective treatment (probability 0.36 of being the most effective; median rank 2 (95% CrI: 1, 5)), although there was insufficient evidence to differentiate between the interventions. The hazard ratio for a randomly chosen study for a new bisphosphonate is 0.85 (95% PrI: 0.26, 2.81).

### 3.2.4. Wrist fractures

Wrist fracture data were available from 7 RCTs. All treatments were associated with beneficial treatment effects relative to placebo, although the true treatment effects were inconclusive relative to placebo. Risedronate was associated with the greatest effect, HR 0.76 (95% CrI: 0.44, 1.25). Risedronate was likely to be the most effective treatment (probability 0.43 of being the most effective; median rank 2 (95% CrI: 1, 4)), although there was

insufficient evidence to differentiate between treatments. The hazard ratio for a randomly chosen study for a new bisphosphonate was 0.85 (95% CrI: 0.26, 2.81).

Heterogeneity in treatment effects between studies, and between bisphosphonates, is summarised in Table 1. The estimates of between-study standard deviation suggest mild (vertebral, non-vertebral), mild-moderate (wrist, hip) and moderate (hip) heterogeneity in treatment effects between RCTs, respectively. The estimates of between-treatment standard deviation indicate mild heterogeneity in effects between treatments (i.e., the effects of the bisphosphonates are relatively similar) but with considerable uncertainty.

Baseline fracture risk can be used as a proxy for differences in patient characteristics across trials, that may be modifiers of treatment effect, and so introduce a potential source of heterogeneity in the NMA. The effect of baseline fracture risk as a potential treatment effect modifier was explored using meta-regression for all fracture types [14]. Based on a comparison of models with and without an adjustment for baseline risk, and inspection of the regression coefficients, there was no evidence that treatment effect varied with baseline risk for any of the fracture outcomes (see Table 2).

**Table 1: Heterogeneity between studies and bisphosphonate treatments, fracture outcomes.**

fracture type	between-study		Between-treatment	
	standard deviation	95% CrI	standard deviation	95% CrI
<b>vertebral</b>	0.19	(0.01,0.49)	0.18	(0.01,0.89)
<b>non-vertebral</b>	0.09	(0.01,0.31)	0.17	(0.01,0.81)
<b>hip</b>	0.43	(0.23,0.74)	0.19	(0.01,0.62)
<b>wrist</b>	0.28	(0.03,0.65)	0.18	(0.01,0.63)

**Table 2: Meta-regression on baseline fracture risk. Model summary for all fracture outcomes.**

	Fracture type			
	vertebral	non-vertebral	hip	wrist
<b>Baseline risk</b>	0.03(-0.20,0.23)	-0.08(-0.46,0.22)	0.43(-0.79,1.67)	-0.40(-2.82,1.38)
<b>Between-study sd</b>	0.20(0.01,0.52)	0.12(0.01,0.38)	0.4(0.06,0.75)	0.35(0.04,0.75)
<b>Between-treatment sd</b>	0.13(0.01,0.46)	0.13(0.01,0.45)	0.19(0.01,0.63)	0.17(0.01,0.61)
<b>Total residual deviance</b>	40.18	24.28	18.19	13.38
<b>data points</b>	40	28	18	12
<b>DIC</b>	69.78	44.84	32.86	23.75

Compare to model without covariates: DIC of 69.13 (vertebral), 43.04 (non-vertebral), 33.99 (hip), 23.06 (wrist).

### 3.2.5. Femoral neck BMD

The sample mean ages of the participants in each study ranged from 50.5 to 78.5 years, with overall mean 64.1 years. Of the 35 RCTs included in the network, six RCTs included only male participants, 26 female, and three mixed.

The effects of each treatment relative to placebo are presented in Figure 3 and pairwise comparisons between treatments are provided in Supplementary Table 12. All treatments were associated with beneficial treatment effects relative to placebo. Zoledronic acid was associated with the greatest effect, mean difference in percentage change in femoral neck BMD 3.20 (95% CrI: 2.51, 3.85). Zoledronic acid was likely to be the most effective treatment (probability 0.44 of being the most effective; median rank 2 (95% CrI: 1, 5)), although there was insufficient evidence to differentiate between treatments. The difference in mean change relative to placebo for a randomly chosen study for a new bisphosphonate is 2.78 (95% PrI: 0.72, 4.77), with the reported prediction interval allowing for both between-study and between-treatment heterogeneity.

The between-study standard deviation was estimated to be 0.53 (95% CrI: 0.30, 0.86), implying moderate heterogeneity in treatment effects between RCTs. The between-treatment standard deviation was estimated to be 0.56 (95% CrI: 0.19, 1.70), which is indicative of

moderate heterogeneity in treatment effects between bisphosphonates (i.e., the effects of the bisphosphonates are more dissimilar) but with considerable uncertainty.

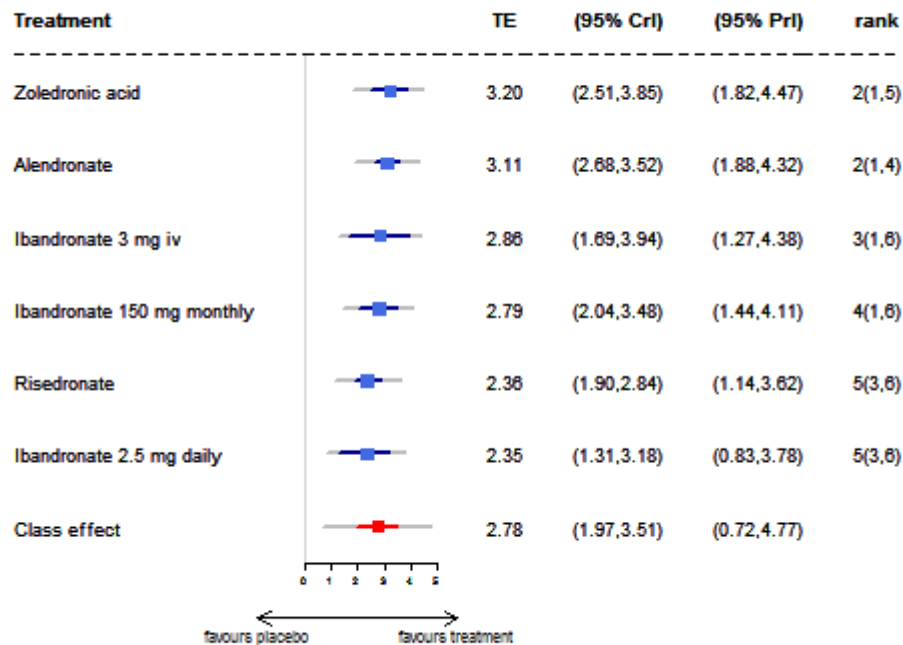
To account for differing trial lengths, study duration was included as a trial level covariate. The estimated impact of duration of study on treatment effect, assuming a common relationship for each treatment, was 0.89 (95% CrI: 0.48, 1.18), indicating an increase in treatment effect with increasing duration of study, as expected.

Based on comparison of models with and without a covariate for mean age, there was no evidence that treatment effect varied with age (Table 3). A meta-regression was conducted to test for different treatment effects according to the proportion of male participants. In line with the licensing indications, a covariate was not included for ibandronate treatments which are not licenced in men. There was no evidence that treatment effect varied by gender (Table 3).

The relationship between baseline response (the response in the placebo arm) and treatment effect was also assessed. There was evidence of an interaction between baseline response and treatment effect, with the interaction term estimated to be -0.46 (95% CrI: -0.76, -0.13) suggesting a larger treatment effect for studies that observed a more rapid decline in BMD under placebo treatment. However, including baseline response did not improve the fit of the model to the data according to a comparison of DICs (Table 6), therefore the evidence is inconclusive.

Within the network there were nine treatment pairs for which both direct and indirect comparison were available. None of the comparisons showed significant evidence of inconsistency as assessed using Bayesian p-values (Supplementary Table 14).

**Figure 3: Mean difference and 95% credible intervals (CrI) for the effect of treatment relative to placebo for percentage change in femoral neck BMD.**



Treatment effects represent the percentage change in BMD for a study of average duration (1.8 years). Blue - pooled effects; Red - class effects; Grey: 95% prediction intervals (PrI). Median ranks and 95% CrI are displayed in the right hand column.

**Table 3: Meta-regression, BMD. Model summary for all meta-regression models.**

	meta-regression model		
	age	gender	baseline response
covariate	0.01(-0.04,0.06)	-0.79(-1.72,0.20)	-0.46(-0.76,-0.13)
between-study sd	0.55(0.31,0.89)	0.47(0.24,0.80)	0.51(0.31,0.78)
between-treatment sd	0.56(0.18,1.73)	0.53(0.18,1.60)	0.5(0.19,1.38)
total residual deviance	53.88	55.26	55.25
data points	59	59	59
DIC*	97.98	97.99	99.33

\* compare to DIC of 96.95 for model without covariates



### 3. Discussion

Network meta-analyses were used to synthesise the evidence and permit a coherent comparison of the efficacy of interventions in terms of fracture and femoral neck BMD for alendronate, ibandronate, risedronate and zoledronic acid. As more RCTs presented data on femoral neck BMD than any of the individual fracture outcome types, the presented BMD network provides a richer evidence base for assessing potential treatment effect modifiers.

The systematic review was based on rigorous methods, with comprehensive searches for evidence, a good level of consistency between reviewers in study selection and double checking of data extraction. A formal assessment of methodological quality of included trial was undertaken. From the assessment of methodological quality, an attrition bias  $\geq 10\%$  across treatment groups was evident for 29 (63%) of the included RCTs. Five trials were reported as either open label or single blind and were considered at high risk of performance bias. Blinded outcome assessment was only reported by 13 (29%) trials. The methodological quality of the evidence base should therefore be taken into consideration when interpreting these results. Although the search strategy for this assessment report was comprehensive, the possibility of a publication bias cannot be discounted. A formal assessment of publication bias was not undertaken.

Adverse event data were widely reported across RCTs but are not reported here. Patient compliance and persistence with treatment was not well reported across RCTs. The majority of included trials typically excluded patients with underlying conditions or receiving medications that affect bone metabolism. Furthermore, patients with a history of or receiving medication for upper gastrointestinal tract disorders were also excluded by the majority of included trials. Therefore, the effects of alendronate, ibandronate, risedronate and zoledronic acid are unknown in these populations.

We included RCTs evaluating current UK licensed doses of bisphosphonate for men and women. Our searches identified only a limited number of RCTs in men. Further research to assess efficacy and tolerability of bisphosphonate treatment in men may be beneficial.

In conclusion, all treatments were associated with beneficial effects on fractures and femoral neck BMD relative to placebo. The ranking of treatments varied across the different outcome types but there was insufficient evidence to differentiate between the interventions. There was some heterogeneity in treatment effects between studies suggesting differential treatment effects according to study characteristics; however, there was no evidence of differential treatment effects with respect to gender and age.

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**Highlights**

- The effectiveness of bisphosphonates for the treatment of osteoporosis was assessed
- Network meta-analysis was used to determine the relative efficacy of treatments
- Outcomes were reduction in fractures and change in bone mineral density
- Beneficial effects relative to placebo were observed for all treatments and outcomes
- No active treatment was significantly more effective for fracture outcomes